

AMENDMENTS TO THE CLAIMS:

Please substitute currently amended claim numbers 1-5, 7-13, 15, 17-19, 23-29, 31, and 52 for the original claims having the same claim numbers.

Please cancel claim number 21 without prejudice or disclaimer.

1. (currently amended) A genetically-modified non-human mammal containing a ~~genetic construct having~~ a single vector comprising a fusion polynucleotide, said fusion polynucleotide comprising a nucleic acid encoding an immunoglobulin component selected from the group consisting of the kappa immunoglobulin light chain, the lambda immunoglobulin light chain, an immunoglobulin heavy chain, and any combination thereof, and a nucleic acid encoding at least ~~one~~ two detectable ~~protein~~ proteins, wherein said non-human mammal is capable of expressing at least one chimeric immunoglobulin gene comprising a polynucleotide sequence encoding at least ~~one~~ at least two detectable ~~protein~~ proteins ~~or peptide~~ fused with ~~a gene expressing an~~ said immunoglobulin component selected from the group consisting of the kappa immunoglobulin light chain, the lambda immunoglobulin light chain, an immunoglobulin heavy chain, and any combination thereof, wherein ~~antibodies~~ an antibody secreted by ~~an immune cells~~ cell of said genetically-modified non-human mammal ~~comprise~~ comprises said at least ~~one~~ two detectable ~~protein or peptide~~ proteins.

2. (currently amended) The genetically-modified non-human mammal of claim 1 wherein said at least ~~one~~ two detectable ~~peptide or protein~~ is proteins encoded by the fusion polynucleotide are present at the C-terminus of the gene product of said fusion polynucleotide.

3. (currently amended) The genetically-modified non-human mammal of claim 2 wherein a polynucleotide encoding said at least ~~one~~ two detectable ~~peptide or protein~~ proteins present at the C-terminus of the gene product of said fusion polynucleotide ~~is~~ are located in exon G1.

4. (currently amended) The genetically-modified non-human mammal of claim 1 wherein said at least ~~one~~ two detectable ~~peptide or protein is~~ proteins are present at the C-terminus of the gene product of said fusion polynucleotide with a flexible linker peptide ~~therebetween~~ located between the at least two detectable proteins and the immunoglobulin component.

5. (currently amended) The genetically-modified non-human mammal of claim 4 wherein a polynucleotide encoding said at least ~~one~~ two detectable ~~peptide or protein~~ proteins present at the C-terminus of the gene product of said fusion polynucleotide with a flexible linker ~~therebetween~~ is between the at least two detectable proteins and the immunoglobulin component is located in exon G1.

6. (previously presented) The genetically-modified non-human mammal of claim 1 wherein said immunoglobulin heavy chain gene is selected from the group consisting of IgG, IgM, IgD and IgA.

7. (currently amended) The genetically-modified non-human mammal of claim 1 wherein an ~~immunoglobulin molecule~~ antibody secreted by ~~an immune cells~~ cell of said genetically-modified mammal comprises at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the heavy chain of said ~~immunoglobulin molecule~~ antibody.

8. (currently amended) The genetically-modified non-human mammal of claim 1 wherein an ~~immunoglobulin molecule~~ antibody secreted by ~~an immune cells~~ cell of said genetically-modified mammal comprises at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the light chain of said ~~immunoglobulin molecule~~ antibody.

9. (currently amended) The genetically-modified non-human mammal of claim 1 wherein an ~~immunoglobulin molecule~~ antibody secreted by ~~an immune cells~~ cell of said genetically-modified mammal comprises at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the heavy

chain and at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the light chain of said ~~immunoglobulin molecule~~ antibody.

10. (currently amended) The genetically-modified non-human mammal of claim 1 wherein at least one ~~said~~ of the at least two detectable ~~protein or polypeptide~~ proteins is capable of quenching fluorescence.

11. (currently amended) The genetically-modified non-human mammal of claim 1 wherein ~~said~~ at least one of the at least two detectable ~~protein or peptide~~ proteins is an autofluorescent protein ~~or peptide~~, a visibly-detectable protein ~~or peptide~~, an enzymatically active protein ~~or peptide~~, or a protein ~~or peptide~~ capable of interacting with another molecule to produce a detectable product, ~~wherein said protein or peptide capable of interacting with another molecule to produce a detectable product is selected from the group consisting of an intein, a biotin-binding subunit of streptavidin or avidin, a His tag, or a chitin-binding domain, or any combination thereof, and wherein said detectable protein may be a single detectable protein or a plurality of detectable proteins, in tandem or not in tandem, optionally separated from the immunoglobulin portion of the polypeptide by one or more linker sequences.~~

12. (currently amended) The genetically-modified non-human mammal of claim 11 wherein ~~said~~ at least one of the at least two detectable ~~protein~~ proteins is an autofluorescent protein ~~or peptide~~.

13. (currently amended) The genetically-modified non-human mammal of claim 11 wherein ~~said~~ autofluorescent protein ~~or peptide~~ is selected from the group consisting of green fluorescent protein, cyan fluorescent protein, yellow fluorescent protein, red fluorescent protein, and a fluorescent analog or fragment of any of the foregoing.

14. (previously presented) The genetically-modified non-human mammal of claim 12 wherein ~~said~~ autofluorescent protein is green fluorescent protein.

15. (currently amended) The genetically-modified non-human mammal of claim 11 wherein said at least one detectable protein is a combination of an autofluorescent protein ~~or peptide~~ and an enzymatically-active protein ~~or peptide~~.

16. (previously presented) The genetically-modified non-human mammal of claim 15 wherein said at least one detectable protein is a combination of green fluorescent protein and alkaline phosphatase.

17. (currently amended) A genetically-modified immune cell ~~produced in vivo and isolated from the genetically modified non-human mammal of claim 1~~ having a single vector comprising a fusion polynucleotide, said fusion polynucleotide comprising a nucleic acid encoding an immunoglobulin component selected from the group consisting of the kappa immunoglobulin light chain, the lambda immunoglobulin light chain, an immunoglobulin heavy chain, and any combination thereof, and a nucleic acid encoding at least ~~one~~ two detectable ~~protein~~ proteins, ~~wherein said at least one detectable protein is present at the C-terminus of the gene product of said fusion polynucleotide with~~ and wherein a flexible linker peptide therebetween is located between the immunoglobulin component and the at least two detectable proteins, and wherein said immune cell is capable of expressing ~~at least one chimeric immunoglobulin gene comprising a polynucleotide sequence encoding at least one~~ two detectable ~~protein or peptide~~ proteins fused with ~~a gene expressing an~~ said immunoglobulin component ~~selected from the group consisting of the kappa immunoglobulin light chain, the lambda immunoglobulin light chain, an immunoglobulin heavy chain, and any combination thereof~~, wherein antibodies secreted by said genetically-modified immune cell comprise said at least ~~one~~ two detectable ~~protein or peptide~~ proteins.

18. (currently amended) The genetically-modified immune cell of claim 17 wherein said at least ~~one~~ two detectable ~~peptide or protein is~~ proteins are present at the C-terminus of the gene product of said fusion polynucleotide.

19. (currently amended) The genetically-modified immune cell of claim ~~18~~ 17, wherein a polynucleotide encoding said at least ~~one~~ two detectable ~~peptide or protein~~ proteins present at the C-terminus of the gene product of said fusion polynucleotide is located in exon G1.

20. (canceled)

21. (canceled)

22. (original) The genetically-modified immune cell of claim 17 wherein said immunoglobulin heavy chain gene is selected from the group consisting of IgG, IgM, IgD and IgA.

23. (currently amended) The genetically-modified immune cell of claim 17 wherein an ~~immunoglobulin molecule~~ antibody secreted by said immune cell comprises at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the heavy chain of said ~~immunoglobulin molecule~~ antibody.

24. (currently amended) The genetically-modified immune cell of claim 17 wherein an ~~immunoglobulin molecule~~ antibody secreted by said genetically-modified immune cells comprises at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the light chain of said ~~immunoglobulin molecule~~ antibody.

25. (currently amended) The genetically-modified immune cell of claim 17 wherein an ~~immunoglobulin molecule~~ antibody secreted by said genetically-modified immune cells comprises at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the heavy chain and at least ~~one~~ two detectable ~~protein or peptide~~ proteins in the light chain of said ~~immunoglobulin molecule~~ antibody.

26. (currently amended) The genetically-modified immune cell of claim 17 wherein at least one of the at least two ~~said detectable protein or polypeptide~~ proteins is capable of quenching fluorescence.

27. (currently amended) The genetically-modified immune cell of claim 17 wherein ~~said~~ at least one of the at least two detectable ~~protein or peptide~~ proteins is an autofluorescent protein or peptide, a visibly-detectable protein or peptide, an enzymatically active protein or peptide, or a protein or peptide capable of interacting with another molecule to produce a detectable product, ~~wherein said protein or peptide capable of interacting with another molecule to produce a detectable product is selected from the group consisting of an intein, a biotin-binding subunit of streptavidin or avidin, a His tag, a chitin-binding domain, or any combination thereof.~~

28. (currently amended) The genetically-modified immune cell of claim 27 wherein ~~said~~ at least one of the at least two detectable ~~protein~~ proteins is an autofluorescent protein ~~or peptide~~.

29. (currently amended) The genetically-modified immune cell of claim 28 wherein ~~said~~ autofluorescent protein ~~or peptide~~ is selected from the group consisting of green fluorescent protein, red fluorescent protein, and a fluorescent analog or fragment of any of the foregoing.

30. (original) The genetically-modified immune cell of claim 29 wherein ~~said~~ autofluorescent protein is green fluorescent protein.

31. (currently amended) The genetically-modified immune cell of claim 27 wherein ~~said~~ at least one detectable protein is a combination of an autofluorescent protein ~~or peptide~~ and an enzymatically-active protein ~~or peptide~~.

32. (original) The genetically-modified immune cell of claim 31 wherein said at least one detectable protein is a combination of green fluorescent protein and alkaline phosphatase.

33. (withdrawn) A hybridoma comprising the genetically-modified immune cell of claim 17.

34. (withdrawn) A chimeric, detectably-labeled immunoglobulin molecule comprising at least one detectable protein or peptide fused with the kappa immunoglobulin light chain, the lambda immunoglobulin light chain, an immunoglobulin heavy chain, or any combination thereof.

35. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 34 wherein said at least one detectable peptide or protein is present at the C-terminus of the gene product of said fusion polynucleotide.

36. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 35 wherein a polynucleotide encoding said at least one detectable peptide or protein present at the C-terminus of the gene product of said fusion polynucleotide is located in exon G1.

37. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 35 wherein said at least one detectable peptide or protein is present at the C-terminus of the gene product of said fusion polynucleotide with a flexible linker peptide therebetween.

38. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 37 wherein a polynucleotide encoding said at least one detectable peptide or protein present at the C-terminus of the gene product of said fusion polynucleotide with a flexible linker therebetween is located in exon G1.

39. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 34 wherein said immunoglobulin heavy chain gene is selected from the group consisting of IgG, IgM, IgD and IgA.

40. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 34 comprising at least one detectable protein or peptide in the heavy chain of said immunoglobulin molecule.

41. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 34 comprising at least one detectable protein or peptide in the light chain of said immunoglobulin molecule.

42. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 34 comprising at least one detectable protein or peptide in the heavy chain and at least one detectable protein or peptide in the light chain of said immunoglobulin molecule.

43. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 42 wherein at least one said detectable protein or polypeptide is capable of quenching fluorescence.

44. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 34 wherein said at least one detectable protein or peptide is an autofluorescent protein or peptide, a visibly-detectable protein or peptide, an enzymatically active protein or peptide, a protein or peptide capable of interacting with another molecule to produce a detectable product, or any combination thereof.

45. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 44 wherein said at least one detectable protein is an autofluorescent protein or peptide.

46. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 45



wherein said autofluorescent protein or peptide is selected from the group consisting of green fluorescent protein, red fluorescent protein, and a fluorescent analog or fragment of any of the foregoing.

47. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 46 wherein said autofluorescent protein is green fluorescent protein.

48. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 44 wherein said at least one detectable protein is a combination of an autofluorescent protein or peptide and an enzymatically-active protein or peptide.

49. (withdrawn) The chimeric, detectably-labeled immunoglobulin molecule of claim 48 wherein said at least one detectable protein is a combination of green fluorescent protein and alkaline phosphatase.

50. (withdrawn) A method for producing a quantity of detectably-labelled polyclonal antibodies comprising the steps of

- a) providing a genetically-modified mammal in accordance with claim 1;
- b) immunizing said genetically-modified mammal with a preselected immunogen, wherein said genetically-modified mammal generates antibodies to said immunogen, wherein antibodies secreted by immune cells of said genetically-modified mammal comprise said at least one detectable protein or peptide; and
- c) isolating said detectably-labelled antibodies from said genetically-modified mammal.

51. (withdrawn) A method for producing a quantity of detectably-labelled monoclonal antibodies comprising the steps of

- a) preparing a genetically-modified mammal in accordance with claim 1;
- b) immunizing said genetically-modified mammal with a preselected

- immunogen, wherein immune cells of said genetically-modified mammal generate antibodies to said immunogen, wherein antibodies secreted by said immune cells comprise said at least one detectable protein or peptide; and
- c) immortalizing antibody-producing immune cells isolated from said genetically-modified mammal;
  - d) selecting immortalized immune cells isolated from said genetically-modified mammal that secrete antibodies specific to said immunogen; and
  - e) preparing a quantity of detectably-labeled monoclonal antibodies from said selected immune cells.

52. (currently amended) A genetically-modified non-human mammal capable of producing a detectably-labeled ~~immunoglobulin~~ antibody in response to immunization by an antigen, the genome of said non-human mammal comprising at least one fusion polynucleotide ~~consisting of~~ comprising a polynucleotide a nucleic acid sequence encoding at least ~~one~~ two detectable ~~protein or peptide~~ proteins fused with a gene ~~and a nucleic acid encoding an immunoglobulin component~~ selected from the group consisting of the kappa immunoglobulin light chain ~~gene~~, the lambda immunoglobulin light chain ~~gene~~, an immunoglobulin heavy chain ~~gene~~, and any combination thereof, wherein ~~an antibodies~~ antibody secreted by ~~an~~ immune cells cell of said genetically-modified non-human mammal ~~comprise~~ comprises said at least ~~one~~ two detectable ~~protein or peptide~~ proteins.

53. (withdrawn) A chimeric, detectably-labeled immunoglobulin molecule comprising at least one fluorescent protein or peptide and at least one fluorescence-quenching protein or peptide fused with a component of said immunoglobulin molecule independently selected from the group consisting of the kappa immunoglobulin light chain, the lambda immunoglobulin light chain, an immunoglobulin heavy chain, and any combination thereof.

54. (new) The method of either one of claims 11 or 27, wherein said protein capable of

interacting with another molecule to produce a detectable product is selected from the group consisting of an intein, a biotin-binding subunit of streptavidin or avidin, a His tag, or a chitin-binding domain, or any combination thereof, and wherein said protein capable of interacting with another molecule to produce a detectable product may also be used to facilitate purification of said detectable product.

55. (new) The method of either one of claims 11 or 27, wherein said detectable protein may be one of at least two detectable proteins or a plurality of detectable proteins, in tandem or not in tandem.